Meeting Report

Modulation of Chemical Toxicity and Risk Assessment

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Manipulation of nutritional factors as a means to reduce human risk from hazardous substances in the environment was the theme of a binational conference hosted by the University of Arizona, College of Pharmacy, Center for Toxicology, in Tucson, Arizona on 9–12 June 1996. This conference was supported in part by grant P42 ES0 4940 from the NIEHS. Additional support was provided by several sponsors from Mexico including the Instituto Nacional de la Nutrición (National Institute of Nutrition), the Centro de Investigación en Alimentación y Desarrollo (Center for Food Research and Development), and the Universidad Autonóma de Qverétaro (Autonomous University of Queretaro). The conference theme, Modulation of Chemical Toxicity and Risk Assessment, provided a forum for more than 100 participants including molecular biologists, toxicologists, geneticists, epidemiologists, nutritionists, and community-based researchers. Formal presentations and poster sessions by scientists from the United States and Mexico focused on five topics: 1) natural toxicants in food, 2) xenobiotic toxicants in food, 3) nutritional status and toxicity, 4) diet modification and toxicity, and 5) policy issues on nutritional modulation and risk assessment. Underscoring the presentations was a concern for the interaction between the diet and chemical toxicity, particularly with regard to using human subpopulations or foreign populations to assess the dose–response relationship of high doses of environmental chemicals. Before epidemiological studies from other countries are used to set limits of exposure in the United States, the effect of factors on dietary chemical toxicity needs to be evaluated, including the effects of regional diets and nutritional status.

Natural Toxicants in Food

Many compounds in the diet can cause toxicity directly or modulate the toxicity of other compounds. The session on natural toxicants in food addressed the effects of mycotoxins, carotenoids, and genistein. Many diseases, including cancer, are diseases of aging, and the major cause of aging is oxidation from by-products of normal metabolism. Ironically, environmental pollutants cause less than 1% of all cancers, while smoking, imbalanced diets, and chronic infections (such as hepatitis) are responsible for 95%. Addressing these three major issues will have a greater impact on decreasing the incidence of cancer than spending billions to address 1% of the risk.

Mycotoxins are by-products of fungal contamination of food crops, most commonly corn, peanuts, and cottonseed. Aflatoxin B_1 is a potent carcinogen that is carefully regulated in food for humans and in feed for livestock. To reduce economic losses, mycotoxin reduction guidelines are being established. These guidelines would allow crops contaminated with mycotoxins to be used after treatment has reduced the mycotoxins to acceptable levels. These guidelines will be very important in Mexico, where the rural, tropical conditions often result in contamination of corn, a major agricultural product and food source.

Aflatoxin B_1 is a highly mutagenic compound. Aflatoxin ingestion in Qidong, China, increases the risk of developing hepatocellular carcinoma (HCC) 2.4-fold. However, aflatoxin B_1 must be metabolized to an epoxide in order to attack DNA. Lycopene, lutein, and ellagic acid, compounds found in the diet, have been shown to modify the metabolism and toxicity of mycotoxins and reduce mutagenicity. This is an example of dietary modification of chemical toxicity.

Other examples of dietary modification of toxicity may be found in cultures with a low incidence of specific cancers, often attributed to dietary intake of various compounds. Asian cultures with diets high in soy have a low incidence of breast cancer. Soy extracts have shown antitumor activity, leading to the study of genistein, a chemical found in soy that has weak activity at the human estrogen receptor. Research indicates that the low incidence of breast cancer may be related to soy but probably not to genistein.

Xenobiotic Toxicants In Food

Humans are exposed to environmental contaminants such as pesticides and heavy metals through contact with the environment and through consumption of contaminated animal or plant products. Presentations in the session on xenobiotic toxicants in food reviewed the observed or potential health effects of xenobiotic toxicants in food.

Pesticides such as DDT and DDE, as well as other compounds in the environment, such as polychlorinated biphenyls and dibenzo-*p*-dioxins, are of concern due to their estrogenic and endocrine disruption properties. The effects of heavy metals are more clearly defined and are often due to interactions with essential metals. Dietary deficiencies may increase gastrointestinal absorption of toxic metals or increase their effects. Ensuring adequate dietary intake of essential nutrients may counter the adverse health effects of toxic metals in at-risk populations.

Although the Mexican government has implemented regulations for many food contaminants, periodic studies indicate that foodstuffs may exceed the allowable limits. Studies in northern Chihuahua and the Mexico City area found that some samples of vegetables, fish, beverages, and other products contained elevated levels of heavy metals such as cadmium and lead. In contrast to the food regulations, the handling of pesticides in Mexico remains unlegislated. According to interviews with agrochemical handlers in the state of Chihuahua, they are at high risk for exposure due to lack of appropriate protection equipment and insufficient training. Clearly, implementation of appropriate training procedures in pesticide handling could lower the risk of exposure.

Poster Discussion

Our understanding of arsenic toxicity in humans relies heavily on epidemiology studies in Taiwan, Mexico, Sweden, the United States, and Chile. This poster discussion session addressed whether the toxic effect of arsenic is influenced by diet, genetic differences, metabolism, or adaptation. This discussion revealed that nutrition indeed plays a role in modulating arsenic toxicity.

Epidemiological studies have cited several dietary factors as being important in the toxicity of arsenic. A comparison of nutritional status between populations in the United States and Mexico demonstrate that the Mexican diet for selected populations provides adequate protein, zinc, and selenium; however, vitamin A intake was one-third lower than that of the selected U.S. population. Therefore, future studies will focus on the significance of inadequate dietary intakes of vitamin A, methionine,

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and choline on the overall metabolism and toxicity of arsenic.

Additional studies were conducted in Bolivia and Mexico on children living in areas of high risk to environmental exposure to lead and arsenic. The results indicated that correcting dietary deficiencies of calcium and iron lessened the absorption of these metals.

Glutathione (GSH), a nutritionally dependent antioxidant, is implicated in the *in vitro* metabolism of arsenic, particularly in the reduction of inorganic arsenate [As(V)] to arsenite [As(III)], the more toxic of the two species. Nutritional modulation of GSH could alter arsenate reduction and in turn affect toxicity by altering the ratio of arsenic species in the body.

Nutritional Status and Toxicity

Nutritional status has been found to influence the development of disease. Comparison of Pima Indian populations in Arizona versus Mexico indicate that diets that are high in fat, processed foods, and alcohol, and low in fiber, fruits, and vegetables lead to increased occurrence of obesity, noninsulin-dependent diabetes mellitus, and stomach cancer.

High intake of animal fat and low intake of calcium and fiber are risk factors for colon cancers. Such diets increase the fecal water concentration of deoxycholic acid, a secondary bile acid shown to be a cancer promoter and to induce DNA damage. Ursodeoxycholic acid (Actigall; Summit Pharmaceuticals, Summit, NJ) was found to decrease the proportion of deoxycholic acid in humans. Further studies in rats have shown that ursodeoxycholic acid inhibits 7-hydroxylase in fecal-type bacteria, thereby decreasing fecal deoxycholic acid by 50% and completely preventing cancer induced by the carcinogen azoxymethane. A high fruit and vegetable, high fiber, low fat diet is being evaluated for reducing the recurrence of breast cancer.

Education, as well as socioeconomic status, influences nutritional status. While poor and isolated populations may suffer from poverty-linked nutritional deficiencies, poor nutritional status also occurs in more affluent sectors due to ignorance-linked excesses such as excessive fat and calorie intake. The link between caloric restriction and decreased tumor occurrence is being investigated. Recent studies in rats, mice, and primates have shown that caloric restriction dramatically increases catalase and superoxide dismutase levels, thereby increasing the ability to protect against the oxygen-free radicals formed during metabolism. Other effects include better DNA repair, higher fidelity in DNA replication, increased apoptosis, and decreased proliferation. Caloric restriction can significantly alter the maximum tolerated dose and toxicity of various compounds.

Diet Modification and Toxicity

Antioxidants and nutrients such as ascorbate, α-tocopherol, selenium, and many other plant-derived compounds such as flavonoids, carotenoids (such as β-carotene), and polyphenols may reduce the risk of certain cancers or degenerative diseases, or alter the toxicity of xenobiotics. Several studies have linked nutrient intake with changes in health status. Selenium supplementation did not protect against nonmelanoma skin cancers but did reduce the incidence of and mortality from carcinomas at several other sites. Topically applied α-tocopherol prevents UV-B induced DNA photodamage, demonstrating its possible utility as a sunscreen. Studies on the effect of β-carotene as a chemoprotective agent in smokers have been inconclusive, although *in vitro* work has shown that β-carotene inhibits smoke-induced lipid peroxidation and that this function is mediated through mechanisms similar to those involved in peroxyl radical scavenging reactions.

Antioxidants, nutrients, and other compounds often exert their protective effects through induction of antioxidant and detoxification enzymes or other proteins. In the rat, induction of hepatic metallothionein by vitamin A is thought to be an essential aspect of tolerance to cadmium hepatotoxicity. Additionally, some phenolic antioxidant food additives induce glutathione-*S*-transferases (GSTs) and quinone reductase, while sulforaphane, the major chemopreventive component of some cultivars of broccoli, inhibits cytochrome P450 enzymes and induces phase II enzymes.

Although vitamin A is an important dietary component, large doses in the rat dramatically increase the hepatotoxicity of chemicals such as carbon tetrachloride. This potentiation is mediated in part by reactive oxygen species released by vitamin A-activated Kupffer cells. High ascorbate supplementation in ascorbate-deficient rats increased chromium (Cr)–DNA binding in liver and kidney compared with low ascorbate supplementation, indicating that ascorbate may be involved in the mechanism of Cr–DNA binding. Although the significance of these studies to human health is unknown, the beneficial effects of diet manipulation or supplementation must be weighed against potentially adverse effects.

Policy Issues on Nutritional Modulation and Risk Assessment

This session included discussion on whether dietary factors that influence chemical toxicity have any impact on the risk assessment process.

As discussed previously, differences in diet and nutritional status may explain differences in the prevalence and severity of chemically induced diseases among populations. Studies in an animal model have shown that methionine, choline, or protein deficiencies result in increased tissue retention of arsenic

and decreased arsenic excretion. Because severe health effects in humans resulting from arsenic exposure have occurred predominantly in populations of low socioeconomic status or whose diets differ greatly from other populations, understanding the influence of diet and nutritional status may lead to better identification of susceptible subpopulations and better risk assessments for diverse populations. Similarly, low folate intake caused increased susceptibility to benzene-induced chromosome aberrations in workers in a region of China. The applicability of this study to risk assessment calculations for this group or other populations in China and around the world may depend on further elucidating the mechanism of benzene toxicity and defining the role of folate and folate deficiency in this mechanism.

Knowledge of the existence and mechanisms of dietary modulation on the status or progression of disease is potentially beneficial in the calculation of human health risk assessments. Such data may be useful in hazard identification as well as in quantifying the dose–response relationship. Clearly, risk assessment methodologies must be refined to permit integration of diverse data sets such as dietary information.

Conclusion

Nutritional modulation has the potential to be a cost-effective method for the amelioration or prevention of chemically induced disease. Several studies presented at this conference support this hypothesis. For example, the more prevalent use of specialized diets involving caloric restriction in cancer bioassay studies indicate that diets lower in fat may indeed help prevent various forms of cancer. Another example is that increases in dietary calcium lessen the degree of toxicity of lead in tortillas made or stored in Mexican ceramic glazed pottery.

It is a simple process to develop a risk assessment for chemicals found in food stuffs. What is missing is a way to factor in nutrient and dietary factors that modulate the toxicity of those chemicals. Developing a clear understanding of the interactions of micro- and macronutrients in the diet with toxicants and incorporating this knowledge into the risk assessment process is a significant challenge for toxicologists. This is a complex problem and may require the development of new modeling techniques to describe these interactions. The effort seems worthwhile because dietary modification is the most significant and cost effective means of modulating chemical toxicity.